STANDARD OPERATING PROCEDURE 41
Blinding and Unblinding in Research Studies

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Contents

Revision Chronology:	Effective date:	Reason for change:
Version 2.0	28 Sept 2022	Minor administrative corrections Addition of reference to protocol templates
Version 1.0	22 July 2020	New SOP created (blinding previously included along with Randomisation procedures – SOP 9). Addition of requirement to complete unblinding forms for emergency and analysis purposes. Addition of requirement to keep unblinding log. Information added on blinding/unblinding methods. Change to new format.

STANDARD OPERATING PROCEDURE 41

Blinding and Unblinding in Research Studies

1. Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to explain the processes involved for blinding and unblinding in research studies and to detail suitable and unsuitable methods.

This SOP is applicable to all University of Warwick personnel involved in the preparation, implementation and use of blinding and unblinding procedures for research studies, unless External Sponsor or other agreed SOPs are to be followed. All templates referenced can be located on the Templates & Guidance page.

2. Definitions

Blinding:	Defined by the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines section 1.10 as: "A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s)."
Unblinding:	The disclosure to one or more of the parties to the study of which intervention the participant received (or was allocated to) during the study.
Placebo:	An inert substance or treatment used in Clinical Trials of Investigational Medicinal Products (CTIMPs) which is designed to have no therapeutic value as a comparator for an active drug. A placebo can be made to look like the active drug to facilitate blinding.
Types of blinding:	
Triple-blind:	A study in which neither the participants nor the person(s) administering the intervention nor the person(s) evaluating the response to the intervention knows which participants are receiving a particular intervention (or lack of intervention).
Double-blind:	A study in which neither the participants nor the person(s) administering the intervention know which participants are receiving the experimental intervention and which are receiving placebo/standard care.
Single-blind:	A study in which one party, either the participant or person(s) administering the intervention, is unaware to which study arm the participant has been allocated.
Open-label or Unblinded:	A study in which the research team and participant know which intervention is being administered.
Assessment blinding:	This is where neither the person administering the intervention or the participant can be blinded, but those assessing crucial outcomes are blinded to the intervention allocated to reduce the introduction of bias.

3. Background

Blinding is the process by which one or more individuals involved in a clinical research study (most commonly a randomised controlled trial (RCT)) are kept unaware of treatment allocation. Although randomisation minimises differences between treatment groups at the outset of the trial, it does nothing to prevent differential treatment of the groups later in the trial nor the differential assessment of outcomes, either of which may result in biased estimates of treatment effects.

The optimal strategy to minimise the likelihood of differential treatment or assessments of outcomes is to blind as many individuals as possible in a trial. Blinding is particularly important when the endpoints of the study are subjective (i.e., assessed by a person) rather than objective (e.g., results of a test). The blinding needs to be robustly protected to maintain the integrity of the data.

Blinding should be preserved wherever possible and unblinding should only be permitted in limited circumstances. The process of emergency unblinding must be included in the study protocol. Having a process to unblind a participant is necessary to protect participants in the event of a medical emergency or for safety reasons. Unblinding of those evaluating the response to the intervention is required in order to interpret the data analysis; this should occur at an appropriate time to ensure bias is not introduced. Documentation of any unblinding events should be retained separately from the rest of the trial documentation until the end of the study or until the final unblinding has occurred for data analysis.

4. Procedure

4.1 Responsibilities

Chief Investigator (CI)	• Determine methods of blinding and emergency unblinding • Ensure testing of unblinding process prior to recruitment • Provide clinical support for unblinding emergencies if required or to ensure a delegate is available for periods of absence • Ensure funding is in place to cover associated costs of unblinding • Ensure all unblinding events are documented
Principal Investigator (PI)	• Delegation of suitable people to request/ perform unblinding • Test unblinding process at site • Ensure appropriate documentation of unblinding at site in Investigator Site File (ISF) and Case Report Form (CRF) • Maintenance of blinding at investigator site
Statistician	• Support CI to develop methods of blinding and unblinding • Document unblinding for analysis by completing the Statistician Unblinding Form and filing in the Study/Trial Master File (S/TMF)
Study/Trial Manager (S/TM)	• Liaise with Investigational Medicinal Product (IMP) manufacturers/suppliers to determine procedures for packaging and blinding of IMP if applicable • Prepare Working Instructions for unblinding procedures and training of Investigators. • Provide access to unblinding systems (inc. back-ups)

	• Coordinate procedures to maintain and monitor the integrity of the blind in accordance with the protocol and Monitoring Plan • Ensure the testing of emergency unblinding processes are documented in the S/TMF • Ensure completed unblinding request form(s) are retained in the S/TMF, and copies are sent to the PI for inclusion in the Investigator Site File (ISF) / Pharmacy File (PF) • Ensure all occurrences of unblinding are documented in the study unblinding log • Consolidate unblinding events at the end of study
Programmer/Randomisation service provider	• Develop and implement an automated unblinding system if required • Coordinate the testing of the automated unblinding system prior to the start of the study
Monitor	• Monitor the integrity of unblinding processes at routine monitoring visits and report any concerns to the Study Manager/CI
Investigator Site Pharmacist ***(In some CTIMPs only)***	• Perform unblinding if required and delegated to do so on local delegation log • Receive and retain unblinding code-breaks for purposes of manual back-up unblinding (where applicable) • Store unblinding code-breaks securely in pharmacy department (where applicable)

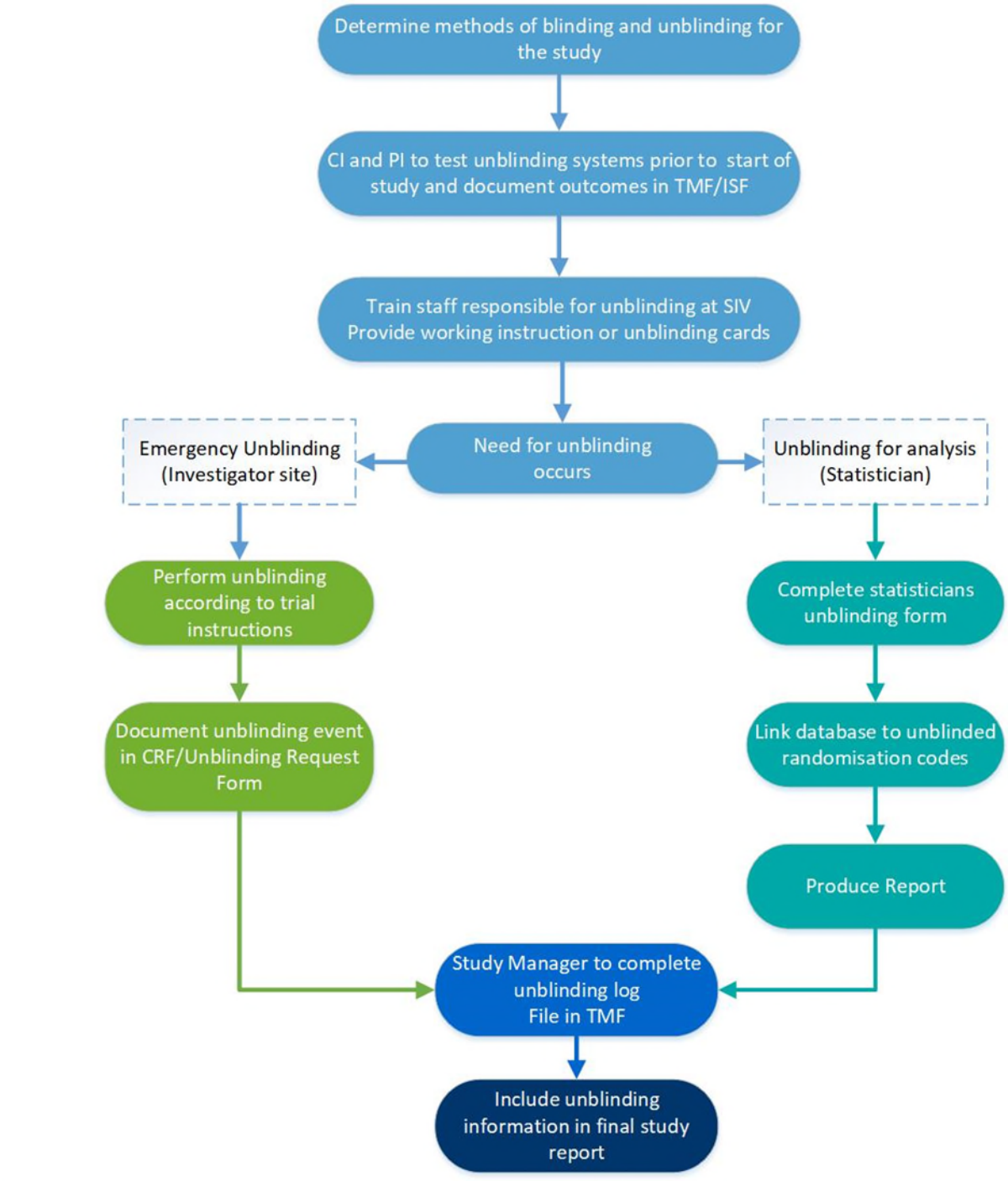
4.2 When?

The type of blinding and any unblinding processes should be determined during the design phase of the study and clearly documented in the approved protocol. For detail of expected content, see relevant protocol writing templates T15 (non-CTIMP) & T16 (CTIMP).

Emergency unblinding can occur under controlled and limited circumstances whilst the study is ongoing. An Unblinding Request Form (Template Ref: T42) should be completed and stored in the relevant section of TMF for each instance.

Unblinding for interim or final analysis should occur after the data freeze (interim) or data lock (final). Final analysis unblinding should be done after approval of the Statistical Analysis Plan (SAP). The statistician should complete the **Statistician Unblinding Form** (Template Ref: T43).

4.3 How?



Abbreviations:
CI – Chief Investigator
CRF – Case Report Form
PI – Principal Investigator
SIV – Site Initiation Visit
TMF/ISF – Trial Master File/ Investigator Site File

4.3.1 Blinding

Blinding relates to the masking of the intervention allocation to one or more parties involved in a clinical research study.

- Type of blinding and methods should be determined by the CI and included in the protocol. Some examples of methods and considerations for maintaining integrity are listed in table 1 of the Appendix at the end of this SOP.
- Blinding should be considered during the initial risk assessment and as part of the monitoring plan to build in appropriate risk control strategies.
- Even despite careful consideration, situations may arise when some or all groups of individuals simply cannot ethically or practically be blinded.
- Where robust blinding cannot be achieved, researchers must incorporate other strategies to minimise bias ensuring that the allocation groups are treated as equally/identically as possible in care provided(except of the intervention itself) before, during and after the intervention is given.
- Special consideration should be given for subjective outcome measures and ensuring balance across each strata depending on the nature of the study.

4.3.2 Emergency Unblinding

4.3.2.1 When is it appropriate to unblind

Emergency unblinding is the process for unblinding one or more participants in a clinical research study. Emergency unblinding, if applicable, should only be permissible for the following reasons:

Knowledge of the intervention allocation is necessary for ongoing treatment or there is a compelling medical or safety reason

Enable assessment of causality & expectedness for reporting potential Suspected Unexpected Serious Adverse Reactions (SUSARs) or related and unexpected SAEs (non-CTIMPs)

4.3.2.2 Methods of emergency unblinding

The protocol for a study with a blinded intervention allocation must include detailed information about ***how*** to unblind, ***when*** unblinding can be done, and ***by whom***.

The protocol should contain detail on the following with regards to emergency unblinding:

- Details of where the unblinded lists are located and their associated security
- Clear process for how to initiate emergency unblinding
- Responsibilities, delegation and training for unblinding
- Details of back-up or out-of-hours systems

In addition to protocolised procedures, it might be appropriate to create a set of **working instructions** which contain detail on where and how to document unblinding events. It might be the case that untrained members of staff who are not part of the trial team will need to unblind e.g. a doctor at another hospital. Where this will be the case, emergency unblinding information cards should be considered, as well as putting unblinding information on any drug packaging. There are many different

ways in which unblinding can be set up depending on the nature and complexity of the study. Some information on methods for unblinding are listed in the Appendix in table 2.

4.3.2.3 Key considerations for emergency unblinding

Immediate:	Where future treatment decisions need to be made quickly there needs to be a mechanism for unblinding 24 hours a day; this should be immediate and should not include approval steps, which may cause delays.
Back-up:	If the primary route of unblinding fails, there should be a back-up system. Where there is a system in operation for working hours, another system should be in place for out-of-hours unblinding if there is a requirement for 24-hour unblinding.
Tested:	All systems should be tested by both the coordinating centre and the investigator sites prior to commencement of randomisation and periodically throughout the trial. Documentation should be filed in the S/TMF and or ISF to demonstrate testing was done.
One-by-one disclosure:	The process of unblinding should be such that the data for only one patient is disclosed at any one time.
Limit disclosure:	If a participant is unblinded for medical reasons, if at all possible the allocation information should be given directly to the participant's health care provider and should not be revealed to site or other staff unless absolutely necessary.
Withdrawal not a requirement:	If a participant has been unblinded to site staff, the participant should be encouraged to remain on the trial, and if at all possible, on their allocated intervention unless medically contraindicated.
Blinded onward reporting:	Developmental Safety Update Reports should provide information on SUSARs in an unblinded format but the CI should not see any other unblinded data so where any reports are to be viewed by the CI, blinded versions should be provided and access to unblinded reports restricted.
Documented:	Each case of emergency unblinding and any attempts to unblind should be documented; see section 4.3.2.4 below.

4.3.2.4 Documentation of emergency unblinding events

There are 4 key places where emergency unblinding events should be documented:

Case Report Form (CRF):

- Who, why, when and the outcome of every unblinding request must be documented in the participant's CRF. Where possible, completed by the person making the request.
- A template **Unblinding Request Form** (Template ref: T42) is availible

Audit trails:

- An audit trail should be available at site pertaining to any unblinding carried out during the study.
- Automated unblinding systems will have an in-built audit trail.

Unblinding Log:

- There should be an **Unblinding Log** (Template ref: T44) at the coordinating centre to document all unblinding requests and events.

Final report:

- Any occurrence of unblinding of individual participants, including the reason(s), must also be documented in any final study reports to funders or in relevant papers.

4.3.3 Unblinding of the study for analysis

Any unblinding processes that will occur during the study for the purposes of analysis should be outlined in the protocol.

4.3.3.1 Interim analysis and safety monitoring

- When performing safety and interim analyses of blinded trials, the integrity of the blind should be maintained, with the exception of the Data Monitoring Committee (DMC) who will have access to partially or fully unblinded data in the closed part of the report. The Study Statistician(s) preparing the DMC report will also require access to partially or fully unblinded data in order to prepare the report.
- Unblinding for the purposes of interim, safety and final statistical analyses should take place according to a pre-agreed process. This can be in the Statistical Analysis Plan (SAP), Protocol or DMC Charter as appropriate.
- Any linking of the unblinded randomisation code to the blinded data should be documented using the **Statistician Unblinding Form** (Template Ref: T43).

4.3.3.2 Unblinding on completion of study

- The details of the unblinding process should be detailed in the protocol.
- When unblinding of the trial for analysis, the **Statistician Unblinding Form** (Template Ref: T43) should be completed to document the timing of the actions, the reason for the request and who performed the unblinding.
- The completed form should be shared with the Programming team.

- The Study Statistician should liaise with the S/TM to ensure that unblinding for the purposes of statistical analysis is listed on the **Unblinding Log** (Template ref: T44).

4.3.3.3 Premature unblinding of the study

- Premature full unblinding is rare but may be required if there are safety concerns. This must only occur by majority vote of the Trial Steering Committee (TSC) or as documented in the trial protocol. The process will be documented in the S/TMF.
- The date and time of linking the final analysis dataset to the unblinded code should be documented on the **Statistician Unblinding Form** (Template Ref: T43) and **Unblinding Log** (Template Ref: T44).

4.3.4 Accidental unblinding

Inadvertent unblinding should be documented as a protocol violation and may constitute a serious breach of GCP and the trial protocol. Where this occurs, a non-compliance report should be produced and appropriate corrective and preventive actions put in place to ensure integrity of the study is maintained and no further accidental unblinding occurs (see SOP 31 'Handling non-compliances, research misconduct and serious breaches of GCP and/or Study Protocol').

4.3.5 End of study procedures

- Review and reconciliation of scratch cards/code break envelopes (if used) should be undertaken at routine monitoring visits and again at the end of the trial.
- The final version of the unblinding log should be reviewed for completeness and all instances of unblinding of intervention allocation should be listed in the final report.
- The study team should determine if it is appropriate to inform participants of their blinded random allocation after completion of the study and at what time point this will be done if there is long term follow-up. If participants are aware of their allocation, consideration for the impact on long term follow-up data should be considered. If participants will be informed, consideration should be made early on for the method:
    - In some situations "Dear Participant" letters will be appropriate.
    - In settings where mailing letters is not possible or appropriate, it will be necessary to plan for disclosure of allocation to participants in person.

List of abbreviations

CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRF	Case Report Form
DSUR	Developmental Safety Update Report
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ISF	Investigator Site File
IMP	Investigational Medicinal Product
IVRS	Interactive Voice Recognition Service
IWRS	Interactive Web Response System
PF	Pharmacy File
PI	Principal Investigator
PPI	Patient and Public Involvement
QA	Quality Assurance
RCT	Randomised Controlled Trial
R&IS	Research & Impact Services
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
S/TM	Study/Trial Manager
S/TMF	Study/Trial Master File
TSC	Trial Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
WCTU	Warwick Clinical Trials Unit

Template Documents

T42	Unblinding Request Form
T43	Statistician Unblinding Form
T44	Unblinding Log
T15	Protocol Template (non CTIMP)
T16	Protocol Template (CTIMP)

Appendix

Table 1. Examples of some **common blinding methods** and considerations for maintaining integrity.

Method	Description	Maintaining integrity	Study types
Independent assessors/ adjudication committees	*Those assessing subjective outcome measures are kept independent of those delivering intervention*	• Physical access restrictions • Electronic access restrictions (with audit trail) • Security of data transfer	Interventional CTIMP Surgical
Over encapsulation	*Deliberate disguising of the identity of a drug allocation by enclosing the placebo/comparator and tested IMP in matching capsules*	• Matching expiry dates, batch numbers and packaging • Reduce numbering allocation patterns on drug packs so that they are random • Data masking: Obvious known side effects of tested IMP can break the blind. Consider this when designing CRF content, requesting lab reports and deciding which SAEs will be reportable • Physical access restrictions • Electronic access restrictions (with audit trail) • Shipping times and documentation	CTIMP
Placebo-to-match	*Deliberate disguising of the identity of a drug allocation by production of a bespoke placebo to match that of the active drug in both external/internal appearance and mode of delivery*		CTIMP
Scar size matching or sham incisions	*If one intervention requires a bigger incision or incisions in different locations – ensuring they match in size and location*	• Sham incisions can pose ethical questions; check with PPI and ethics committee	Surgical
Concealment of incisions	*Use of coverings to hide differences in incisions which may reveal allocation*	• This may only work for assessors	Surgical
Digital alteration of scans	*Redaction of items in a digital scan which may reveal allocation to the assessor*	• Physical access restrictions • Electronic access restrictions (with audit trail) • Security of data transfer	Surgical

Table 2. Examples of emergency unblinding methods

Requirement for 24/7 cover	Methods	Considerations
NO	Code-break envelopes	• Works well for single-site, non-complex interventions. • In the event of an unblinding event, the person unblinding will need to open the tamper proof envelope, sign and date/time stamp it.
	Scratch cards	• Similar concept to unblinding envelopes above. • Easy to see if scratch cards have been tampered with; this helps with assurance of integrity. • External vendor required.
	Tear-off labels	• Sealed tear-off label on the study drug that is placed in the medical notes upon dispensing. • Accessed via medical notes and unblinding is required. • Difficult for sites using electronic medical records.
YES	Telephone unblinding	• Centralised system where the person requesting calls to speak to someone who facilitates the unblinding process. • In order to provide a 24-hour service, this usually needs to be outsourced to a specialised company. These companies will manage the whole process and usually employ staff with clinical expertise.
	Interactive Voice Recognition Service (IVRS)	• Centralised system where the person requesting calls and unblinds by responding to various automated prompts over the phone. • This system does not need any additional man-power and can be implemented 24 hours a day but a back-up will be required.
	Interactive Web Response System (IWRS)	• Centralised system where the person requesting logs into a web-based application and proceeds through a number of questions until it provides the allocation. • This system does not need any additional man-power and can be implemented 24 hours a day but a back-up will be required.